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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,020	05/24/2001	Steven I. Dworetzky	3053-4091US1	4756

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EXAMINER

MURPHY, JOSEPH F

ART UNIT	PAPER NUMBER
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1646

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/866,020

Applicant(s)

DWORETZKY ET AL.

Examiner

Joseph F Murphy

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 January 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-78 is/are pending in the application.
- 4a) Of the above claim(s) 25-57, 61 and 63-78 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 16, 20 and 24 is/are allowed.
- 6) ☒ Claim(s) 1-15, 17-19, 21-23, 58-60 and 62 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5, 6.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: Sequence Comparison A,B.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-24, 58-60 and 62, drawn to an isolated nucleic acid sequence of SEQ ID NO: 1, encoding SEQ ID NO: 2 in Paper No. 8, 10/15/2002 is acknowledged. The traversal is on the ground(s) that the protein of SEQ ID NO: 2 is a related invention and does not impose an undue burden on the Examiner to search both Groups. This is not found persuasive for the following reasons.

Applicant's attention is directed to MPEP 808.02 which states that "Where the related inventions as claimed are shown to be distinct under the criteria of MPEP 806.05 (c-i), the examiner, in order to establish reasons for insisting upon restriction, must show by appropriate explanation one of the following: (A) Separate classification thereof; (B) A separate status in the art when they are classifiable together; (C) A different field of search." As set forth in the Restriction requirement, Group I is classified in class 435, subclass 69.1; Group II is classified in class 530, subclass 350. The separate classification established for each Group demonstrates that each distinct Group has attained recognition in the art as a separate subject for inventive effort, and also a separate field of search. Thus, the Restriction requirement is proper.

Applicant argues that no burden is placed on the examiner to consider all claims. As discussed above, the separate classification established for each Group demonstrates that each distinct Group requires a separate field of search, and a search of one Group would not reveal art on the other Groups, thus imposing a burden on the examiner.

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The requirement is still deemed proper and is therefore made FINAL. Claims 1-78 are pending. Claims 25-57, 61, 63-78 are withdrawn from consideration pursuant to 37 CFR 1.142(b). Claims 1-24, 58-60, 62 are under consideration.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-15, 17-19, 21-23, 58-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid of SEQ ID NO: 1, encoding SEQ ID NO: 2, does not reasonably provide enablement for a polynucleotide encoding a KCNQ5 protein, nucleic acids which are 80% identical to SEQ ID NO: 1, polynucleotides which hybridize to a nucleic acid encoding SEQ ID NO: 2, a polynucleotide which is an allelic variant, or a splice exon variant of the polynucleotide encoding the protein encoded by SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-15, 17-19, 21-23, 58-60 are overly broad since insufficient guidance is provided as to which of the myriad polynucleotides which the claims encompass, will retain the characteristics of KCNQ5 activity. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors considered to be relevant in the instant case are set forth below:

(1) the breadth of the claims - The claims are drawn to polynucleotide encoding a KCNQ5 protein, nucleic acids which are 80% identical to SEQ ID NO: 1, polynucleotides which hybridize to a nucleic acid encoding SEQ ID NO: 2, a polynucleotide which is an allelic variant, or a splice exon variant of the polynucleotide encoding the protein encoded by SEQ ID NO: 1. In the specification, the term KCNQ5 polynucleotides are defined as encompassing mutants by substitution, deletion, insertion, inversion or addition in the encoded polypeptide (page 20, lines 1-15). Thus, the claims encompass nucleotides which encode variant proteins.

(2) the nature of the invention - The instant invention is a polynucleotide.

(3) the state of the prior art - Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). The Voet reference demonstrates that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Thus, the amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and

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functional requirements of the encoded proteins are lacking, it is unpredictable as to which encoding variations, if any, meet the limitations of the claims.

(5) the level of predictability in the art - The Voet reference demonstrates the unpredictability of the protein art.

(6) the amount of direction provided by the inventor - Applicant has only taught SEQ ID NO: 1, encoding SEQ ID NO: 2. Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of KCNQ5.

(7) the existence of working examples – No working examples are provided for variant polynucleotides encoding SEQ ID NO: 2.

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(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Given the breadth of claims 1-15, 17-19, 21-23, 58-60 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 41-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

These are genus claims. The claims are drawn to polynucleotide encoding a KCNQ5 protein, nucleic acids which are 80% identical to SEQ ID NO: 1, polynucleotides which

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hybridize to a nucleic acid encoding SEQ ID NO: 2, a polynucleotide which is an allelic variant, or a splice exon variant of the polynucleotide encoding the protein encoded by SEQ ID NO: 1.

In the specification, the term KCNQ5 polynucleotides are defined as encompassing mutants by substitution, deletion, insertion, inversion or addition in the encoded polypeptide (page 20, lines 1-15). Thus, the claims encompass nucleotides which encode variant proteins. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to SEQ ID NO: 1. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claims 7-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a host cell in culture comprising a polynucleotide with the sequence as set forth in SEQ ID NO: 1, does not reasonably provide enablement for *in vivo* transfection.

The specification on page 25 discloses that the nucleic acids of the current invention can be expressed in a wide variety of host cell types, including cells within a host animal. However, there are no actual or prophetic examples that disclose how to make or use host cells that comprise a DNA sequence as set forth in SEQ ID NO: 1 in an animal. The Examiner cites Eck & Wilson (page 81, column 2, second paragraph to page 82, column 1, second paragraph) who report that numerous factors complicate *in vivo* gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. Since the instant disclosure does not address any of the methods necessary to make a host cell in an animal which comprises the polynucleotide of interest, the claims as written are not enabled.

Claim 62 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The deposit of the biological material is considered necessary for the enablement of the current invention (see MPEP Chapter 2400 and 37 C.F.R. §§ 1.801-1.809). Elements required for practicing a claimed invention must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. Applicants have provided the deposit number for the plasmid encoding KCNQ5 on page 19 of the specification, however, the specification is not fully compliant with all of the provisions for maintenance and availability of the deposited material. If a deposit is made under the terms of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g. see 961 OG 21, 1977), and Applicants, their assignee or their agent needs to provide a declaration containing the following: i) a statement all restrictions on the availability to the public of the deposited material so deposited will be irrevocably removed upon the granting of a patent. ii) A statement that the material has been deposited under conditions that assure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. 1.14 and 35 U.S.C. § 122. iii) A statement that the deposited material will be maintained with all of the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case, for a period of at least thirty years after the date of deposit or for the enforceable life of the patent, whichever period is longer. iv) A statement by declarant that all statements are true and that all statements made on information and belief are believed to be true; and further that these statements were made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are

punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-15, 17-19, 21-23, 58-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14 and 15 recite the term "stringent conditions", which is a conditional term and renders the claim indefinite. Furthermore, some nucleic acids which might hybridize under conditions of moderate stringency, for example, would fail to hybridize under conditions of high stringency. The metes and bounds of the claim thus cannot be ascertained. This rejection could be obviated by supplying specific conditions supported by the specification which Applicant considers to be "moderately" or "highly" "stringent". Claims 18, 19, 22, 23 are rejected insofar as they depend on the recitation in claims 14 and 15 of "stringent conditions".

Claim 1 is vague and indefinite in the recitation of the terms "KCNQ5". There is no definition within the claim to define the protein to which these acronyms refer. Thus, the metes and bounds of this claim cannot be determined. Claims 2-15, 17-19, 21-23, 58-60 are rejected insofar as they depend on the recitation in claim 1 of "KCNQ5"

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-12, 14-15, 17-19, 21-23, 58-59 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 9907832 (Blonar et al.).

Blonar et al. teaches the cloning and expression of two potassium channel proteins, KCNQ2 and KCNQ3 (page 2, lines 21-29). The nucleic acid and amino acid sequence of KCNQ2 is set forth in Figures 2A and 2B. A comparison of the nucleic acid sequence of the nucleic acid sequence claimed as SEQ ID NO: 1 and the nucleic acid sequence encoding KCNQ2 is set forth in Sequence Comparison A, attached. A comparison of the amino acid sequence of KCNQ2 and the amino acid sequence encoded by SEQ ID NO: 1 is provided in Sequence Comparison B. The nucleic acid encoding KCNQ2 anticipates claims 1 and 2 because it encodes an amino acid sequence comprising a portion of KCNQ5 of SEQ ID NO: 2. Claim 3 is anticipated because the KCNQ2 polynucleotide comprises a portion of SEQ ID NO: 1. Claims 4-12, 17-19, 21-23, 60 are anticipated because Blonar et al. teaches vectors and host cells comprising the KCNQ2 polynucleotide (pages 15-17). Claims 14-15 are anticipated because the KCNQ2 polynucleotide would hybridize under to conditions set forth in the claims to SEQ ID NO: 1. Claims 58-59 are anticipated because KCNQ2 is an allelic variant of SEQ ID NO: 1.

Conclusion

Claims 1-15, 17-19, 21-23, 58-60, 62 are rejected.


Claims 16, 20, 24 are allowable.

Advisory Information


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
March 31, 2003



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